

**REMARKS**

Favorable reconsideration of the above-identified application in view of the amendments above and the remarks following is respectfully requested.

Claims 87, 90, 92, 94, 95, 97, 99-102, 104, 112 and 113 are pending in the application. Of the above claims, 87, 90, 92, 94, 95, 97, 99-102, 104, 112 and 113 have been rejected. Claims 92, 95, 99, 100 and 104 have now been cancelled. Claims 87, 90, 94, 97 and 102 have now been amended.

***35 U.S.C. § 112 Rejection 1<sup>st</sup> paragraph Rejections***

The Examiner has rejected Claims 87, 90, 92, 94, 97, 99-102, 104 and 112-113 under 35 U.S.C. § 112 first paragraph for failing to comply with the written description requirement. Specifically, the Examiner states that citing an accession number in a claim is improper incorporation of reference of essential subject matter into the claims.

Examiner's rejections are respectfully traversed.

Claims 99-100 and 104 have now been cancelled, rendering moot Examiner's rejection to these claims.

Please note that the Accession number for TAK1 has now been removed from the claims rendering moot Examiner's rejections.

The Examiner has rejected Claims 87, 92, 94, 95, 99-102 and 104 under 35 U.S.C. § 112 first paragraph for failing to comply with the written description requirement. The Examiner states that the specification does not provide an adequate written description of the vast genus of agents that are capable of modulating the activity of a SMAD protein.

Examiner's rejections are respectfully traversed.

Please note that Claims 99-100 and 104 have now been cancelled, rendering moot Examiner's rejection to these claims.

In the interest of a speedy prosecution, the agents of Claim 87 have been limited to those which are referred to in the specification:

1. Polynucleotides capable of hybridizing with TAK 1 are referred to in paragraph 87.

2. Polypeptides encoded by polynucleotides as set forth in SEQ ID NO: 1 and 2 are referred to in paragraphs 94-96.
3. Polypeptide homologs are referred to in paragraph 97.
4. Polynucleotides as set forth in SEQ ID NOs: 1 and 2 are referred to in paragraph 101.
5. Polynucleotides encoding homologs are referred to in paragraph 102.

Claim 94 have been limited to polynucleotide agents capable of down-regulating an expression of TAK1 and polynucleotide agents or polypeptide agents capable of suppressing an interaction of TAK1 with an MH2 domain of the SMAD protein.

Polynucleotides capable of downregulating expression of TAK 1 are referred to in the specification. For example paragraph 84 refers to antisense oligos, paragraph 86 refers to siRNAs and paragraph 87 refers to oligos capable of hybridizing with endogenous TAK1 ds DNA.

Claim 102 have now been amended to limit the agents which are capable of suppressing an interaction of TAK1 with an MH2 domain of the SMAD protein to those which are referred to in the specification, as detailed above for Claim 87:

The Examiner has rejected Claims 87, 90, 92, 94, 95, 97, 99-102, 104 and 112-113 for failing to comply with the enablement requirement. The Examiner states that the only intended use for a method of regulating SMAD proteins in a cell is for regulating osteogenesis and/or bone repair. The Examiner further states that the claims are broad as they read on using a genus of cells, SMAD proteins and agents and further the claimed method embraces decreasing or increasing a genus of activities of a SMAD protein. The Examiner continues that only several SMAD proteins are activated by bone morphogenetic protein (BMP) so it is unclear how all SMAD proteins can be used in the method since some are not involved in BMP-mediated SMAD activity resulting in osteogenesis and/or bone repair. The Examiner further states that the Claim 92 is only enabled for mesenchymal stem cells. Furthermore, the Examiner states that the specification does not provide sufficient enablement for administering cells at any site in the subject. In addition, the Examiner states that the specification does not describe examples showing that down-regulation of TAK1 in vivo is effective in inducing osteogenic differentiation.

The Examiner's rejections are traversed.

Please note that Claims 95, 99-100 and 104 have now been cancelled rendering moot Examiner's rejection to these claims.

In order to expedite speedy prosecution of this case, various amendments have been made to Claims 87 and 94 in order to overcome Examiner's rejection.

1. The cells have now been limited to mesenchymal stem cell.
2. The methods have now been limited to contacting the cells *in vitro* with an agent of the present invention.
3. The agents have now been limited to polypeptide or polynucleotide agents.
4. In Claim 94, the treated cell is now administered to a bone of the subject.
5. In Claim 94, the SMAD protein has been limited to SMAD2. Support for such a limitation can be found on Page 46, paragraph 197.

In view of the above arguments and claim amendments, Applicant believes to have overcome these 35 U.S.C. § 112 rejections.

### ***35 U.S.C. § 103 (a) Rejection***

The Examiner has rejected claims 87 and 90 under 35 U.S.C. 103(a) as being unpatentable over Bartelmez et al (US 6,841,542) taken with Sugita et al WO99/40202 and Sano et al (The Journal of Biological Chemistry 274:8949-8957, 1999).

The Examiner states that Bartelmez et al teaches use of an antisense oligomer directed against TGF-B in cells. The Examiner further states that Sano et al teaches that TGFB is upstream of pathways comprising TAK1 and SMADs, and thus inherently down-regulation of TGFB will result in downregulation of TAK1. Although Bartelmez et al does not specifically teach that TAK 1 was present in the cells, Sugita et al teaches that TAK1 of SEQ ID NO: 11 is present in cells.

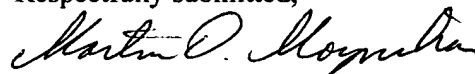
The Examiner's rejection is respectfully traversed.

In order to expedite speedy prosecution of this case, the agents of Claim 87 have been limited to polynucleotide agents capable of hybridizing to TAK1 and TAK1 deletion mutants of SEQ ID NO; 1 or 2 (either as polypeptides or polynucleotides encoding same).

In view of these amendments, Applicant maintains that the art of Bartelmez et al cannot be used to anticipate the presently claimed invention either alone or in combination with Sano et al or Sugita et al.

In view of the above amendments and remarks, it is respectfully submitted that claims 87, 90, 94, 97, 101-102 and 112-113 are now in condition for allowance. An early Notice of Allowance is respectfully and earnestly solicited.

Respectfully submitted,



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**Enclosures:**

- Petition for Extension (Three Months)